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NEPHROLOGY FORUM

Hypertensive nephrosclerosis in African Americans

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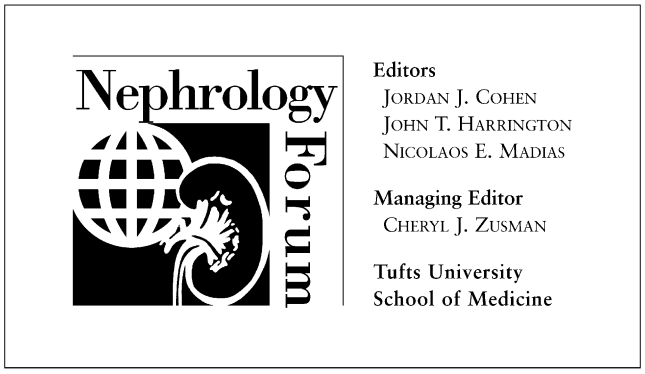

CASE PRESENTATION

A 67-year-old black man presented with a 7-year history of hypertension. He smoked 2 packs of cigarettes per day for 20 years but quit completely after a stroke 4 years ago. He was employed as a maintenance man, and his annual household income was less than $14,000. The patient had been treated intermittently with antihypertensive agents, but follow-up had not been consistent, and scant records of blood pressure recordings indicated inadequate control (>140/>80 mm Hg). After the stroke 4 years ago, he was hospitalized with right-sided hemiparesis that resolved completely. He had been treated intermittently for gout with colchicine and nonsteroidal anti-inflammatory drugs. His medications at presentation were atenolol, 100 mg/day; hydrochlorothiazide, 25 mg/day; and triamterene, 10 mg/day. He was advised to adhere to a low-salt diet but admitted that he did not comply.

The family history was significant. The patient's father died of a stroke while on maintenance hemodialysis; his end-stage renal disease (ESRD) was attributed to hypertension. The patient's mother was alive and had type 2 diabetes, hypertension, and a history of myocardial infarction. He had two sisters and one brother. One sister and one brother were hypertensive, but neither was known to have target organ damage. The patient's 45-year-old son has hypertension and takes antihypertensive medication.

At presentation, the patient's blood pressure was 210/130 mm Hg; pulse rate, 68 beats/min; height, 1.8 m (5 feet, 10 inches); weight, 90 kg (198 pounds). He had grade 2 hypertensive retinopathy, an S4 gallop, and pitting pretibial edema. No tophi were present, and his neurologic examination was normal. An electrocardiogram revealed left-ventricular hypertrophy. Fasting laboratory data included: blood urea nitrogen (BUN), 28 mg/dL; serum creatinine, 2.4 mg/dL; sodium, 140 mEq/L; potassium, 4.6 mEq/L; chloride, 104 mEq/L; total CO_2, 23 mmol/L; calcium, 9.2 mg/dL; phosphorus, 4.3 mg/dL; albumin, 4.2 g/dL; total cholesterol, 238 mg/dL; low-density lipoprotein (LDL) cholesterol, 155 mg/dL; triglyceride, 202 mg/dL; uric acid, 8.1 mg/dL; aspartate aminotransferase (AST), 23 IU; alanine aminotransferase (ALT), 30 IU; alkaline phosphatase, 110 IU; and total bilirubin, 1.0 mg/dL. A complete blood count revealed 5800 white blood cells/mm^3; hemoglobin, 14.3 g/dL; packed red blood cells, 41%; and a normal platelet count. Hepatitis serologies, including HB_sAg and HCV RNA, were negative. Urinalysis revealed a specific gravity of 1.021; pH, 5.0; 1+ protein; and no abnormal cells, casts, or crystals. A 24-hour urine collection contained 1.65 g creatinine; protein, 1056 mg; and sodium, 269 mEq. Serum protein electrophoresis was normal, and urinary protein electrophoresis disclosed nonselective proteinuria. Glomerular filtration rate (GFR), estimated by iothalamate clearance, was 55 mL/min/1.73 m^2.

The patient was treated with atenolol, 100 mg once daily; furosemide, 40 mg twice daily; and verapamil, 240 mg twice daily. He was followed closely at intervals of 1 to 3 months and subsequently every 3 to 6 months. Antihypertensive medication was titrated frequently to maintain his blood pressure in the range of 130–140 mm Hg systolic and 80–85 mm Hg diastolic. During the first 24 months of follow-up, his serum creatinine remained

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Key words: essential hypertension, systolic hypertension, end-stage renal disease, microalbuminuria, AT_1-receptor antagonists, ACE inhibitors, renin-angiotensin-aldosterone system.

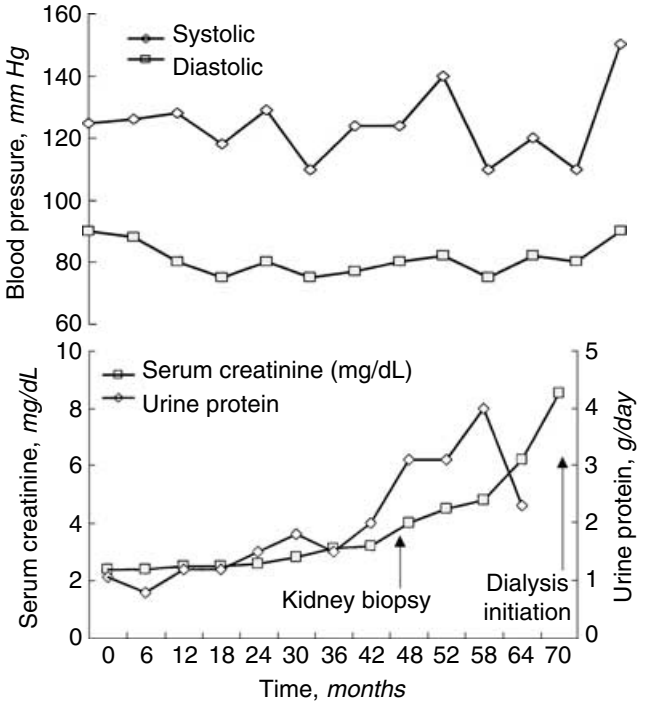

Fig. 1. Clinical course of patient with biopsy-proven hypertensive nephrosclerosis.

relatively stable in the range of 2.5 to 2.8 mg/dL (Fig. 1). His average blood pressure during this period was 128/81 mm Hg. Despite continued blood pressure control in the range of 110–140/75–85 mm Hg, his serum creatinine gradually increased. At a clinic visit 36 months after initial evaluation, his serum creatinine was 3.1 mg/dL, and the 24-hour urinary protein excretion had increased to 1.5 g. No change in treatment was recommended. At a clinic visit 48 months after initial presentation, physical examination revealed a blood pressure of 130/80 mm Hg; an S4 gallop; and trace pretibial edema. The serum creatinine was 4.1 mg/dL; 24-hour urine protein, 3.0 g; and urinary sodium, 196 mEq/day. Serum and urine protein electrophoreses were unrevealing.

A renal biopsy was performed. Light microscopy disclosed arteriolar sclerosis and hyalinosis, global and focal glomerular sclerosis, and evidence of glomerular ischemia (simplification). Also present were interstitial fibrosis with tubular atrophy and chronic interstitial inflammation, findings consistent with the diagnosis of hypertensive nephrosclerosis. Immunofluorescence and electron microscopy revealed findings consistent with hypertensive nephrosclerosis. The patient's medications were not changed. Despite continued adequate blood pressure control, his renal function continued to deteriorate, and hemodialysis was initiated 72 months after his initial visit.

DISCUSSION

Dr. Robert D. Toto (*Professor of Medicine, University of Texas Southwestern Medical Center, Dallas, Texas, USA*): Hypertensive nephrosclerosis is an important public health problem. A heterogeneous disease, its pathogenesis and pathophysiology are incompletely understood. On average, the rate of progression is relatively slow as compared with diabetic nephropathy, some glomerulonephritides, and autosomal-dominant polycystic kidney disease. Treatment includes pharmacologic lowering of blood pressure with an angiotensin-converting enzyme (ACE) inhibitor, whenever possible. Additional modifiable risk factors beyond blood pressure control and inhibition of the renin-angiotensin-aldosterone system are important in patient management. Last, future studies are needed to improve detection, diagnosis, and treatment. Let's look at each of these key points in turn.

Epidemiology

Approximately 6% of patients with essential hypertension have chronic kidney disease and are at risk for progression to ESRD [1]. Hypertension is cited as the cause of ESRD in approximately 30% of new cases in the United States [2] and is the second leading cause of ESRD in African Americans. The incidence of hypertensive nephrosclerosis is increasing; however, the rate of increase has decreased somewhat in the past 5 years [2]. The reason for this rate decrease is not clear, but it might represent reclassification of hypertensive nephrosclerosis as diabetic nephropathy or other renal disease. Moreover, the incidence of ESRD attributed to hypertension is fivefold higher in African Americans than in non-African Americans [2–4]. The health care costs for managing ESRD attributed just to hypertension exceed $1 billion annually.

In general, hypertension in African Americans develops at an earlier age, is more severe, and is more difficult to control. Thus it is not surprising that ESRD attributed to hypertension generally occurs at a younger age in African Americans as compared to non-African Americans [2]. Epidemiologic and case-control studies have demonstrated increased risk for hypertension as a cause of ESRD in the United States [5–13] and in Australian aborigines [14]. Factors that might account for racial disparity in ESRD attributed to hypertension include a lack of access to medical care, socioeconomic status [7, 15–18], severity and duration of hypertension [1, 19–22], education level [7, 22, 23], alcohol and drug abuse [24, 25], genetic predisposition [26–31], and nephron endowment [32–37]. The National Health and Nutrition Examination Survey II indicates that modifiable risk factors, including sociodemographic, lifestyle, and clinical factors, "explain" less than one-half of the increased risk for ESRD in

Table 1. Risk factors for hypertensive nephrosclerosis

Age (older than 50 years)
Male gender
African American race
Systolic hypertension
Dyslipidemia
Family history
Duration of hypertension
Severity of hypertension
Proteinuria
Decreased glomerular filtration rate
Low socioeconomic status
Decreased nephron number
Cigarette smoking

African Americans [22, 38, 39]. In this analysis, the unadjusted relative risk of ESRD among African Americans was 2.96 and after adjustment for these factors decreased to 1.96 but remained significant. Therefore, other risk factors, including genetic determinants, likely play an important role in predisposing African Americans to ESRD.

Risk factors

Numerous risk factors influence the onset and progression of hypertensive nephrosclerosis (Table 1). Today's patient had most of these. He was an older black male with longstanding hypertension, a family history of renal disease, low socioeconomic status, a history of cigarette smoking, severe systolic hypertension, advanced chronic renal disease, and dyslipidemia.

Systolic hypertension is a powerful predictor of the development of ESRD [40]. Analysis of the impact of systolic hypertension among 334,000 men screened for the Multiple Risk Factor Intervention Trial (MRFIT) indicated that systolic hypertension was an independent risk factor for all-cause ESRD. Moreover, the relationship between systolic blood pressure and the development of ESRD was graded and consistent throughout the range of blood pressures recorded at the time of screening into the study [41]. In addition to data from MRFIT, the Atherosclerosis Risk in Communities (ARIC) observational study [23], the Hypertension Detection and Follow-Up Program (HDFP) [1], the Systolic Hypertension in the Elderly Program (SHEP), and the VA Cooperative Trial report that systolic blood pressure is an independent risk factor for ESRD attributed to hypertension [21, 40, 42]. Systolic hypertension has been overlooked as a major risk factor for renal and cardiovascular outcomes in hypertensive populations [43]. With the exception of studies specifically focused on systolic hypertension, such as the SHEP, clinical trials in cardiovascular and renal disease have utilized diastolic or mean arterial pressure as the parameter for titrating antihypertensive drugs. Future studies should focus on control of systolic blood pressure to reduce risk of hypertension complications, including chronic kidney disease.

Proteinuria is recognized as an important risk factor for progression of both diabetic and nondiabetic renal disease [44–48]. In a small cohort of 77 patients with hypertensive nephrosclerosis, we demonstrated that, as compared to those with a urinary protein excretion <500 mg/day, patients with a higher daily urinary protein excretion exhibited a significantly faster rate of decline in GFR [44]. Similarly, patients with a urine protein/creatinine ratio >0.22 enrolled in the African American Study of Kidney Disease and Hypertension (AASK) exhibited a twofold higher rate of decline in GFR as compared with those with lower protein excretion rates [3].

Decreased glomerular filtration rate also has been associated with an increased risk for ESRD. In the AASK trial, although blood pressure was controlled to levels as low as 127/77 mm Hg, renal disease continued to progress in patients (GFR level <40 mL/min/1.73 m^2 and proteinuria >300 mg/day) with hypertensive nephrosclerosis [3, 4, 44].

Dyslipidemia is a common finding in patients with hypertensive nephrosclerosis. Several lines of evidence implicate this as a risk factor for chronic kidney disease. In the ARIC study, hypertriglyceridemia and low plasma levels of high-density lipoprotein (HDL) were associated with the onset of hypertensive renal disease [23]. Hypercholesterolemia was associated with the development of ESRD in the MRFIT [10, 25]. In addition, hypercholesterolemia correlates with global glomerulosclerosis in patients with biopsy-proven hypertensive nephrosclerosis [49]. Moreover, LDL-cholesterol, small dense LDL, and hypertriglyceridemia are associated with renal disease progression [50, 51]. However, no clinical trials have indicated that lipid-lowering therapy reduces the risk for onset or progression of hypertensive nephrosclerosis. It therefore seems reasonable to use current nationally accepted guidelines for lipid-lowering therapy in hypertensive nephrosclerosis [52, 53].

Cigarette smoking has been associated with an increased rate of decline in renal function in diabetics and patients with hypertensive nephrosclerosis [54–57]. The mechanisms by which cigarette smoking likely contributes to renal dysfunction have been reviewed elsewhere [54].

Pathogenesis

The pathogenesis of hypertensive nephrosclerosis is complex and incompletely understood. A genetic predisposition to renal injury in the setting of hypertension and reduced nephron number have been postulated as important factors in the development and progression of hypertensive nephrosclerosis. Indeed, animal studies and human linkage analyses support the hypothesis that a genetic susceptibility to renal disease exists in patients with chronic renal disease. Rat models of hypertensive

nephrosclerosis suggest that several genes predispose the kidney to renal injury, and mouse models of lupus nephritis indicate that genetic susceptibility is an important contributing factor to the development of renal disease [30, 31, 58–65]. However, to date no gene or group of genes has been linked to the development and progression of hypertensive nephrosclerosis in humans. Mapping of rat gene Rf-1 in humans has yielded varying success [64, 65]. A recent analysis indicated that a region near a selected marker adjacent to the human homologue of the Rf-1 gene contributes to ESRD susceptibility in African Americans [65]. It is likely that multiple genes are involved in the predisposition to renal injury in African Americans, and future studies have been designed to identify such associations. Although candidate genes of the renin-angiotensin-aldosterone system have been studied, the available data do not indicate a strong likelihood that any of the components of this system are pathogenetic in human hypertensive nephrosclerosis [66].

Several studies suggest that reduced nephron number and nephron hypertrophy play a role in the development of hypertension and the progression of renal disease [33–37, 67], but this has not been shown to be a definitive cause of kidney disease. Hypertension can cause renal vascular injury, including ischemia and hypertrophy of glomeruli, vessels, and tubules. Interstitial inflammation and fibrosis are important components of the histopathologic lesions observed in hypertensive nephrosclerosis and probably derive in part from hypertensive injury [49]. Simultaneous afferent arteriolar vasoconstriction and vasodilation involving different nephron populations might contribute to hypertensive renal damage. Afferent vasoconstriction might cause glomerular and tubular ischemia and lead to glomerular simplification and thereby loss of filtration surface area as well as tubular atrophy and tubulointerstitial inflammation/fibrosis, all histologic features common in hypertensive nephrosclerosis [49, 67]. In contrast, afferent vasodilation in remnant nephrons of individuals with hypertension, especially those with low nephron number, can cause glomerular hypertension and associated glomerulosclerosis, proteinuria, and progressive renal failure [32, 68–72].

Angiotensin II plays an important role in the progression of hypertensive nephrosclerosis. In animal models, inhibition of angiotensin II synthesis or blockade of the angiotensin type-1 receptor reduces blood pressure, renal injury, proteinuria, and progression of kidney disease [3, 4, 68, 72–76]. In humans with hypertensive nephrosclerosis, lowering blood pressure with an ACE inhibitor reduces proteinuria and preserves renal function [3, 47, 74–77]. Taken together, these data strongly support a critical role for angiotensin II in the progression of hypertensive nephrosclerosis.

Table 2. Pathologic lesions in hypertensive nephrosclerosis

Arteriosclerosis and arteriolosclerosis
Medial hypertrophy
Intimal fibrosis
Hyalinosis
Global glomerulosclerosis
Segmental glomerulosclerosis
Tubulointerstitial changes
Tubular atrophy
Inflammation
Fibrosis

Diagnosis

The definition of hypertensive nephrosclerosis is not based on rigorously developed criteria [66]. I have defined hypertensive nephrosclerosis as nondiabetic chronic kidney disease associated with chronic (often stage 3) hypertension, with or without moderate proteinuria, and a pathologic picture characterized by arteriosclerosis, arteriolosclerosis, glomerulosclerosis, and interstitial fibrosis in the absence of immune deposits. It is important to recognize that, like diabetic nephropathy and in contrast to various glomerulonephritides, the diagnosis of hypertensive nephrosclerosis is generally based on clinical criteria, not renal biopsy criteria. The reason is that very few individuals with chronic renal disease or ESRD attributed to hypertension, that is, hypertensive nephrosclerosis, undergo a renal biopsy. Therefore, the diagnosis of hypertensive nephrosclerosis is almost always based on history, physical examination, urinalysis, and serologic testing. Indeed, the major reason for pathologic identification of hypertensive nephrosclerosis is that clinicians perform a renal biopsy based on clinical suspicion of glomerulonephritis because of proteinuria [66, 75]. It is important to note, however, that clinical criteria can be strongly associated with the histopathologic lesion of hypertensive nephrosclerosis [49, 75]. In patients undergoing renal biopsy for research purposes, nondiabetic hypertensive African Americans with mild to moderate renal insufficiency in the absence of marked proteinuria were overwhelmingly likely to have renal vascular lesions consistent with the clinical diagnosis of hypertensive nephrosclerosis [49] (Table 2). Thus, middle-aged African Americans with longstanding moderate to severe hypertension, stage 3 chronic kidney disease (GFR < 60 mL/min), and urine protein/creatinine ratio < 2.5 are likely to exhibit renal pathology consistent with hypertensive nephrosclerosis. Nevertheless, unselected patients with a clinical diagnosis of hypertension are frequently discovered to have a renal disease other than hypertensive nephrosclerosis [75]. In African Americans with hypertensive nephrosclerosis, solidified global glomerulosclerosis is more common than in white patients with hypertensive nephrosclerosis [78]. Despite

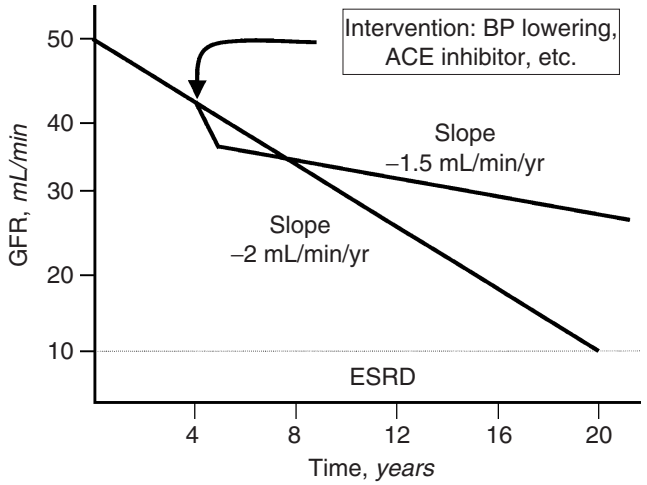

Fig. 2. Decline in glomerular filtration rate (GFR) of hypothetical patient with hypertensive nephrosclerosis. The rate of decline in GFR is 2 mL/min/year. Intervention that improves BP, inhibits ACE, etc., may slow this rate.

the fact that hypertension is identified as the cause of ESRD in almost 30% of incident patients in the United States today, a vanishingly small number of these cases have had this diagnosis confirmed by renal biopsy. This is important because (*1*) an overestimation of hypertensive nephrosclerosis and, hence, an underestimation of other renal diseases is possible, and (*2*) no rigorous criteria exist for the diagnosis of hypertensive nephrosclerosis, including histologic criteria. It is clear that a better definition for the phenotype of hypertensive nephrosclerosis is needed.

Rate of progression of kidney disease

The rate of progression of hypertensive nephrosclerosis is relatively slow. The rate of decline in GFR is similar in diabetic nephropathy and polycystic kidney disease, 5–6 mL/min/year [45–48]; the rate in proteinuric patients with nondiabetic nephropathies is the highest, 6–8 mL/min/year [47]. Among common renal diseases, treated hypertensive nephrosclerosis has the slowest average rate of decline in glomerular filtration rate, 1–2 mL/min/year [4, 44]. Figure 2 illustrates the impact of this rate of decline on a hypothetical patient with treated hypertensive nephrosclerosis. As shown in the figure, a 50-year-old man with a baseline GFR of 50 mL/min would develop ESRD requiring dialysis in 20 years, or at age 70. Interventions that reduce this rate of progression might prevent ESRD and the need for dialysis.

Treatment

Clinical trials of management of hypertensive nephrosclerosis are few. Only the AASK prospectively examined the impact of clinical management on renal outcomes in patients with hypertensive nephrosclerosis. Previous large-scale clinical trials in hypertensive patients designed to examine the impact of blood-pressure-lowering on cardiovascular disease [1, 8, 79–83] had only a few renal events. The HDFP demonstrated that the likelihood of deterioration in renal function was higher in the patients whose blood pressure was less strictly controlled [1]. Ad hoc analyses of the MRFIT demonstrated that the likelihood of deterioration in renal function was greater in African Americans despite similar blood pressure control as in whites [8, 79]. Clinical management studies consisting of mixed chronic kidney disease populations also demonstrated that stricter blood pressure control was associated with a reduced likelihood of progression of renal disease [40, 84, 85]. In a long-term follow-up study of hypertensive patients, Perry et al demonstrated that in patients with a decrease in systolic blood pressure by more than 20 mm Hg, the rate of ESRD was decreased by nearly two-thirds [40]. These data were suggestive but not conclusive that blood-pressure-lowering in hypertensive patients reduces the likelihood of ESRD. However, none of these studies specifically focused on hypertensive nephrosclerosis with established chronic kidney disease, and the multicenter trials were not designed to examine renal outcomes.

We previously reported the results of a single-center trial involving 77 patients with hypertensive nephrosclerosis that was specifically designed to examine the impact of blood-pressure-lowering on the rate of decline in GFR estimated by renal clearance of iothalamate [44]. In our study, hypertensives with a GFR <70 mL/min (range 15–70 mL/min) were randomly assigned to one of two blood pressure groups: strict control or diastolic blood pressure <80 mm Hg, and conventional control or diastolic blood pressure of 85–90 mm Hg. All participants entered into the trial had their blood pressure lowered to <80 mm Hg prior to randomization. Participants were followed for about 40 months; decline in GFR was the primary outcome. We found that the average rate of decline in both groups was not significantly different from zero and there was no difference between groups despite a significant 6 mm Hg difference in achieved diastolic blood pressure. There were 7 of 42 and 2 of 35 cases of ESRD in the strict and conventional blood pressure groups, respectively, rates that were not significantly different. Rates of decline in GFR among African Americans and non-African Americans were not significantly different despite significantly higher achieved diastolic blood pressures in African Americans. This study provided strong and convincing evidence that long-term lowering of blood pressure in high-risk patients (mostly African American males) with moderate to severe hypertension, hypertensive nephrosclerosis, and GFR of 30–60 mL/min is associated with a very slow average rate of decline in GFR, not different from that of aging. Moreover, the data suggested that lowering blood pressure in African Americans to a similar degree as in whites was not associated with a more

Table 3. African American Study of Kidney Disease and Hypertension (AASK) study design: Randomization scheme

	Drug class[a]		
	Metoprolol	Amlodipine	Ramipril
Usual blood pressure goal	20%	10%	20%
Lower blood pressure goal	20%	10%	20%
Combined *number*	441	217	436

[a] Percentage represents proportion of study cohort randomized to indicated study group. For example, 10% of the cohort was randomized to the usual blood pressure goal and amlodipine.

rapid decline in renal function. However, this small trial did not show different rates of decline at lower blood pressure and was not designed to examine the effect of different antihypertensive agents on outcome.

The AASK trial was designed to answer two important questions. Does aggressive lowering of blood pressure result in slower decline in renal function? Does the type of antihypertensive agent used to lower blood pressure affect renal outcomes [86]? The study was a prospective, randomized, double-blind controlled trial utilizing a 2 × 3 factorial design (Table 3). Nondiabetic African Americans age 18 to 70 years with a clinical diagnosis of hypertensive nephrosclerosis, a diastolic blood pressure ≥95 mm Hg, GFR in the range of 20–65 mL/min/1.73 m^2, and a urine protein/creatinine ratio <2.0 were enrolled in the trial. They were randomized to one of two levels of blood pressure control and one of the following: metoprolol (control group), ramipril, or amlodipine. Additional antihypertensive agents were added to achieve blood pressure goals; patients were followed for up to 5 years (mean follow-up, 3.4 years). The primary outcome was the rate of decline in GFR, and the secondary outcome was a composite of a rapid decline in GFR (50% reduction or 25 mL/min absolute reduction from baseline), ESRD, or death from any cause. The results of the blood pressure comparison groups revealed no significant difference between the lower blood pressure and the usual blood pressure group in the rate of decline in GFR or in the secondary composite outcome. It is important to note that achieved mean arterial blood pressure was about 10 mm Hg lower in the lower blood pressure group as compared to the usual blood pressure group. This difference was achieved within 6 months and was maintained throughout follow-up. Not even a slight trend suggested that lower blood pressure improved renal outcome. However, a significantly greater increase in proteinuria persisted throughout the study in the usual blood pressure as compared to the lower blood pressure group. Furthermore, for patients with a baseline proteinuria <300 mg/day, assignment to the lower blood pressure group was associated with reduced risk for development of proteinuria >300 mg/day. Whether this difference in proteinuria indicated long-term renal protection for the lower blood pressure group cannot be ascertained from the AASK study. Despite these negative results in the blood pressure comparisons, the outcomes among the drug group assignments revealed important differences. Overall, there were no differences in the rate of decline in GFR among the drug treatment groups. This was in part due to the fact that in the amlodipine group, there was a sharp and significant increase in GFR during the first 6 months of the trial, as compared to the metoprolol control group and the ramipril group. In contrast, the cumulative event rate for the composite outcome of rapidly declining GFR, ESRD, or death was significantly lower in the ramipril as compared either with the metoprolol or the amlodipine groups. There was a 22% risk reduction ($P < 0.042$) for ramipril compared to metoprolol, and 38% for ramipril compared with amlodipine ($P = 0.004$). No difference appeared between the amlodipine and metoprolol groups for the composite outcome. However, for the combined outcome of ESRD and death, treatment with ramipril, as compared to amlodipine, was associated with a 49% risk reduction ($P < 0.01$), and treatment with metoprolol, as compared to amlodipine, was associated with a 42% risk reduction ($P = 0.003$).

Proteinuria is an important risk factor for progression of hypertensive nephrosclerosis and is generally associated with a lower GFR [4, 43, 74, 86]. The AASK trial found a significant interaction between baseline proteinuria and outcomes for both blood pressure control level and drug groups with respect to GFR decline and composite clinical outcome. Baseline proteinuria was a strong predictor of progression of renal disease, and patients with higher proteinuria also had lower baseline GFR. Patients with baseline protein excretion rate >300 mg/day or a urine protein/creatinine ratio of >0.22 had a rate of decline in GFR of approximately 5 mL/min/year as compared to 2 mL/min/year in those with a baseline urine protein/creatinine ratio <0.22. Moreover, the composite clinical end point event rate was nearly 5 times higher in patients with proteinuria at baseline (>300 mg/day) versus nonproteinuric participants. The rate of decline in GFR from entry to completion of follow-up was faster in the proteinuric subgroup. Also, subgroup analysis indicated that both ramipril and metoprolol were associated with a lower composite event rate as compared to amlodipine-treated participants. The results of these and other analyses from this landmark clinical trial likely will provide new insights and directions for future research into hypertensive nephrosclerosis.

QUESTIONS AND ANSWERS

Dr. John T. Harrington (*Division of Nephrology, Tufts-New England Medical Center, Boston, Massachusetts*): Bob, that was a superb review of the complicated pathogenesis of hypertensive nephrosclerosis in African

Americans. One of the problems I've always had with hypertension and progressive kidney failure is the chicken and egg phenomenon. In a recent article in the *New England Journal of Medicine*, Ritz's group compared glomerular counts in kidneys from 10 control patients with counts in kidneys from patients with hypertension [35]. In round numbers, the glomerular counts were 700,000 in the hypertensive group and 1.4 million in the control group. Which comes first? Does hypertension cause the low glomerular count or vice versa? Could you comment on a general level, and specifically on Ritz's data?

Dr. Toto: First of all, I agree with you. I've been working on this problem for about 20 years. I think the chicken and the egg issue is still open. I don't think that the observation of Ritz's group changes that, but it's an important observation. As I pointed out, several studies indicate that nephron number might be lower in certain groups. African Americans have been suggested as one of those groups—maybe they have smaller kidneys, a smaller number of nephrons, more hypertrophic nephrons—and some data have compared blacks to whites, although the studies were limited in scope. In preparation for this Forum, I was amazed to find that in the past 10 to 15 years we still haven't gotten a clear answer about what this disease process is. What you are asking is whether the kidney is being damaged by the hypertension. Maybe African American patients with kidney failure have an intrinsic renal disease causing their hypertension. Biopsy of the kidney with current techniques that we use to characterize the disease is not enough to help make that distinction.

Dr. Harrington: My second question is an epidemiologic one. You looked at studies comparing blacks and whites in the United States. Have comparable studies been carried out in other parts of the world, specifically in Africa or the Caribbean? What, if anything, can we learn from such studies?

Dr. Toto: I'm not aware of any other countries that have looked at this carefully as in the USRDS. South Africa would be the place that one most likely would look. In Australia, Dr. Wendy Hoy looked at differences in aboriginal populations and found a higher incidence of renal failure and ESRD associated with hypertension than in nonaboriginal populations [14]. Dr. Hoy has been characterizing these data epidemiologically and her findings are consistent with the United States data.

Dr. Angelo A. Ucci, Jr. (*Division of Pathology, Tufts-New England Medical Center*): I was interested in your pointing out that the pathologic changes are general ones. They mostly characterize injury to various parts of the renal structures. Do you have a sense about what would make a better diagnostic group of criteria for this disease? A combination of both clinical and pathologic, or new approaches?

Dr. Toto: I think we need better criteria. I think we're going to find better histologic markers that will help us differentiate changes. We might discover histologic or histochemical techniques that uncover endothelial markers or genetic markers in the kidney in these patients. I could only guess at what specific proteins we should look at. Clearly we need better tools to provide diagnostic clarity and specificity to hypertensive patients with chronic renal disease. Perhaps we should perform kidney biopsies in more hypertensive patients.

You might have seen the article from Dr. Fogo's group that came out in *Kidney International* last year in which they compared the histopathology in white patients with that in blacks [78]. They did find some differences, however, as they noted, selection bias might have played a role insofar as it was a retrospective analysis. In their analysis, African Americans had worse renal function at the time of biopsy; that is, their creatinines were 4.0 to 5.0 mg/dL, whereas in whites, creatinine ranged from 2.5 to 3.0 mg/dL. The serum creatinine level is expected to be slightly higher in the African Americans than in the non-African Americans; still, the study could have biopsied some patients at a later stage of (more severe) disease. So the disease looks more severe, but is it really different? If we don't have a marker better than a renal biopsy, perhaps we should do more. The downside is that it might not make a difference therapeutically today. But until we have noninvasive markers, perhaps we should consider a carefully designed study to evaluate renal biopsy to move this field forward. In most cases, we lower the blood pressure, give an ACE inhibitor, and follow the serum creatinine level.

Dr. Dana Miskulin (*Division of Nephrology, Tufts-New England Medical Center*): I wonder whether body mass index, that is, obesity, was independently associated with a faster progression of hypertensive nephrosclerosis in the AASK study.

Dr. Toto: I'm not aware of any convincing epidemiologic data. I've seen some data that suggest that overweight might be a risk factor for renal disease. I don't know that there's any hard data on that–maybe someone in the audience can comment on that. I'm not aware of any studies that have clearly demonstrated that obesity, per se, is a risk factor.

Dr. Miskulin: I also want to ask about the effect of blood pressure control on renal progression. Did the effect of the low blood pressure intervention vary across subgroups with different baseline levels of kidney function? For example, one might hypothesize that no effect or even a detrimental effect was found for individuals with relatively advanced disease (GFR $\sim$ 20 mL/min/1.73 m^2), whereas beneficial effects might be found in those with relatively preserved kidney function (GFR $>$ 45 mL/min/1.73 m^2).

Dr. Toto: I have a couple of comments. First, that is a subgroup analysis so you have to be careful about that. This wasn't a prespecified analysis, as I remember. Second, this was one of the issues that we grappled with during the design of AASK. Shouldn't we start earlier, for example, select patients with a GFR of 80 and follow them long-term? The downside is this: the disease generally progresses slowly, so if you take patients into the trial, most of whom have a decline in GFR of 2 mL/min/year, you have to follow them a very long time. Then what? Should you look at an alternative surrogate outcome or continue to follow GFR?

Dr. Mark Sarnak (*Division of Nephrology, Tufts-New England Medical Center*): You presented results demonstrating that tight blood pressure control did not slow the progression of GFR decline in the AASK study. What is your recommendation to patients regarding target blood pressure? My concern is that most patients with chronic kidney disease die from cardiovascular disease rather than develop end-stage renal disease, and therefore target blood pressure needs to take both risks into account. A related question is whether the follow-up cohort component of the AASK study will have sufficient power to evaluate risk factors for cardiovascular outcomes.

Dr. Toto: You're making an excellent point, namely, that there's "competition" between death or disability from cardiovascular disease and progression of renal disease to end stage. As you know, recent data suggest that people who have a myocardial infarction or stroke might have a higher likelihood of developing renal failure. To answer specifically the issue about the decline in GFR, we are rethinking whether that's the best way to follow patients with kidney disease. There is a lot of debate about what should be the right renal outcome to measure and what size clinical trial will be required to define statistically the number of cardiovascular events. My current recommendation is to achieve and maintain blood pressure in the range of 130–140/75–85 mm Hg in hypertensive nephrosclerosis. The AASK cohort study is tracking cardiovascular disease events and cardiovascular outcomes, including hospitalizations and deaths from any cause, including cardiovascular death. More than 700 patients are being followed currently. The cohort will have adequate power for us to evaluate risk factors.

Dr. Jeanine Carlson (*Division of Nephrology, Tufts-New England Medical Center*): It would appear that once an African American patient has developed hypertensive nephrosclerosis to any degree, the natural history is for it to progress to ESRD despite the adequacy of blood pressure control. If we consider your schematic, where you postulate the progression of this disease (Fig. 2), perhaps we are not identifying patients at risk early enough. Do you think we should be using a stricter definition of hypertension in the African American population, perhaps beginning antihypertensive therapy when the blood pressure is greater than 130/80 mm Hg rather than waiting until it is 140/90 mm Hg?

Dr. Toto: Yes, but this is a personal bias on my part. Remember, the AASK study doesn't show any renal benefit of lower blood pressure comparing 140/85 mm Hg to 127/77 mm Hg. You might ask, "Why would you lower the blood pressure to any more than 140/85 mm Hg?" You might need to add more blood pressure medicines to achieve a lower level of blood pressure but the patient still remains at higher risk for a stroke or myocardial infarction. The cardiovascular event rate in AASK was too low to show a difference between the two levels of blood pressure compared. Specifically, if I don't start treating a patient's blood pressure earlier than we currently do, perhaps damage is already ongoing and irreversible. We do not know this, but we need to find out whether it is true.

Dr. Ronald Perrone (*Division of Nephrology, Tufts-New England Medical Center*): How would you integrate the results of the ALLHAT trial with the AASK trial? My understanding is that the African Americans in the ALLHAT study perhaps did worse on ACE inhibitors in terms of blood pressure control.

Dr. Toto: The ALLHAT population is considerably different than the AASK study population. Most of the patients in the AASK study were already taking several antihypertensive medications when they came in. Most of the patients in the AASK trial could not have their blood pressure controlled with a thiazide diuretic or one other agent. As I said earlier, many AASK study patients didn't have much of a response to hydrochlorothiazide and needed additional agents. As far as doing worse, our AASK data show that when you give an ACE inhibitor in the context of "adequate" blood pressure control in this patient population, it is more protective than a beta blocker or calcium channel blocker. Obviously, giving an ACE inhibitor is not enough. We did two things. We blocked ACE and lowered the blood pressure substantially in these patients. Maybe the ACE inhibitor is the better antihypertensive agent when used in conjunction with these other drugs. In HOPE study participants who had undergone ambulatory blood pressure measurement, ramipril, given at night, caused a 10 mm Hg reduction in nocturnal blood pressure compared to the placebo group.

Dr. Perrone: In a 30-year-old hypertensive African American with a creatinine of 1.2 mg/dL and a blood pressure of 140/90 mm Hg, what would be your drug of choice?

Dr. Toto: I would like to know whether the patient has an abnormal urinalysis and especially whether proteinuria is present. My approach would be to use an ACE inhibitor if proteinuria is present. The ALLHAT study would suggest using a thiazide in a patient with a creatinine of 1.2 mg/dL, and that might be fine as long as the blood pressure is controlled to 130 mm Hg systolic.

Dr. V. S. Balakrishnan (*Division of Nephrology, Tufts-New England Medical Center*): Getting back to pathogenesis, could you speculate on the role of transforming growth factor-β1 (TGF-β1) or plasminogen activator inhibitor-1 (PAI-1) in this disease, especially in light of the recent polymorphisms that have been identified in their genes?

Dr. Toto: That's an excellent question. As you know, plasma levels of TGF-β are higher in some African Americans than in whites in some studies. Cytokines are important in the development of fibrosis of the blood vessels and in the kidneys of these patients. I'm not sure that variations in the genes that are controlling the specific cytokine are really going to be important in the pathogenesis of hypertensive nephrosclerosis. We are finding more and more cytokines and that makes it very difficult to select one or two as the critical cytokine. If you did have to pick one gene, I'd speculate that it is the gene for angiotensin II. One can think of angiotensin II as a cytokine because it has so many nonhemodynamic effects, as well as its better-known hemodynamic effects.

Dr. Harrington: Let me ask a hypothetical question. If you were advising the director of the NIH on clinical trials in nephrology and you're allowed only $60 million for two trials, what two studies would you choose?

Dr. Toto: I would probably spend my money on one study because they're getting so expensive now. I would look at cardiovascular disease outcomes in a chronic renal disease population. I would spend the money on either hypertension or diabetes, or common diseases that we see that account for this huge disease burden and the associated health care cost. I would do a longer study with a larger number of patients without a lot of measures of GFR that would cost me a lot of my budget.

If I were going to perform two studies, then I would do one study in the pre-ESRD chronic renal disease population and the other in the dialysis population using the end point of all-cause mortality. I would try to reconstruct something like the statin trial using a drug that you could give to most patients, and I would make inclusion criteria relatively simple. I would try to think outside the box in terms of clinical trials. Instead of measuring GFR, which is terribly expensive, difficult to interpret, and variable, I would try to imitate the HOPE trial in a renal population. That is, I like the idea of taking 2000 or 3000 dialysis patients and giving one-half of them a statin and the other half placebo or vitamin E and seeing whether we can reduce morbidity and mortality. The best example that I can think of is the SPACE trial from Israel in which patients given vitamin E, 800 units, showed a reduction in secondary cardiovascular events [87]. That study desperately needs to be confirmed. Vitamin E is relatively inexpensive and it's safe.

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